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- (72) **Inventors; and**
- (71) **Applicants :** MILLER, Leonard, B. [US/US]; 27 Devon Road, Brookline, MA 02467 (US). DEVORE, Dale, P. [US/US]; 3 Warwick Drive, Chelmsford, MA 01824 (US).
- (74) **Agents:** JANIUK, Anthony, J. et al.; Lathrop & Gage LLP, 28 State Street, Boston, MA 02109 (US).
- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,

DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

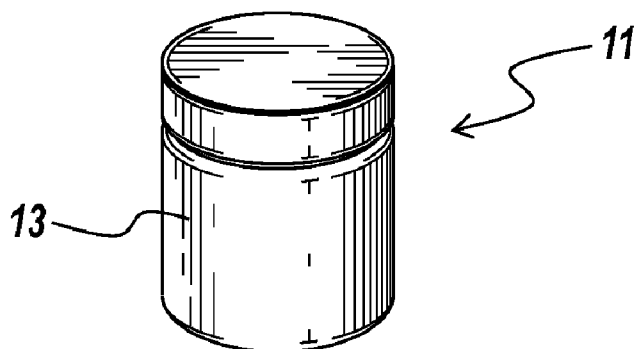
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- (88) **Date of publication of the international search report:**  
29 January 2015

(54) **Title:** METHODS AND ARTICLES OF MANUFACTURE FOR THE TREATMENT OF SKIN



**Fig. 1**

(57) **Abstract:** Embodiments of the present invention are directed to methods and articles of manufacture to treat skin to improve and/or increase hydration, pliability, and thickness for improved texture, feel and appearance. Embodiments feature applying an effective amount of an acetylation agent to natural dermal collagen under reaction conditions to react the natural dermal collagen with the acetylation agent to form a modified collagen. The modified collagen has a higher net charge and higher net charge density than natural dermal collagen. The modified collagen improves or increases one or more skin characteristics consisting of hydration, pliability and thickness.



**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/US 14/32951

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC(8) - A61B 19/00; A61M 31/00 (2014.01)  
 CPC - B29K 2105/04; B29C 44/5636; B01D 69/02  
 According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**  
 Minimum documentation searched (classification system followed by classification symbols)  
 CPC (A61K33/00; A61P31/04; A61K31/40; A61K36/185; A61K36/232; A61K38/17; A61K31/525; A61K9/00; A61K2800/88; A61M35/006; A61K8/0208; A61Q19/00; A61Q17/04; B05B7/0823; A61M35/003; B05B7/162)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
 USPC (128/898; 604/522; 424/94.1; 424/94.67; 424/722; 514/415; 548/510; 424/773; 514/21.2; 514/251; 424/725; 604/290; 206/223; 401/132; 239/70)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 PatBase, Google Patents/Scholar - Terms: acetylation acylation agent reagent skin topical dermal alkaline base oil collagen hydration pliability thickness immediately before application treatment jet spray pad foil packs suspension cosmetic penetration enhancer EDTA concentration net-charge-density just prior right fat sulfonic acids OR anhydrides

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2005/0106270 A1 (DEVORE et al.) 19 May 2005 (19.05.2005) para [0013], [0014], [0023], [0028], [0030], [0034], [0041], [0043]; abstract	1-5, 7-8, 13-16, 18-22, 24-25 and 30-34 ----- 6, 9-12, 17, 23, 26-29 and 35-40
Y	US 5,248,693 A (GERSPACHER et al.) 28 September 1993 (28.09.1993) col 13, ln 8-14; col 14, ln 8-31	6, 9, 17, 23, 26 and 35
Y	WO 2012/116445 A1 (PURCELL) 07 September 2012 (07.09.2012) para [0011], [0028], [0032], [0033]	10-12 and 27-29
Y	US 5,368,581 A (SMITH et al.) 29 November 1994 (29.11.1994) abstract; col 2, ln 46-33; col 5, ln 21-67; col 6, ln 1-30; col 7, ln 45-55; col 8, ln 57-67; col 9, ln 1-3	36-37 and 39-40
Y	US 2011/0259974 A1 (COOPER et al.) 27 October 2011 (27.10.2011) para [0034], [0038]; abstract	38

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 15 October 2014 (15.10.2014)	Date of mailing of the international search report <b>27 OCT 2014</b>
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young  PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
- 2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
- 3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

---please see continuation in supplemental box ---

- 1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
- 2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
- 3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
- 4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
  - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
  - No protest accompanied the payment of additional search fees.

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BOX III: lack of unity

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: claims 1-17, directed to method of treating skin

Group II: claims 18-40, directed to an article of manufacture, a delivery system for the treatment of skin

The inventions listed as Group I-II do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group I requires a method of treating skin; not required in group II.

Group II requires an article of manufacture comprising a delivery system; not required in group I.

The only technical features shared by Groups I-II that would otherwise unify the groups are treating skin comprising the steps of: applying an effective amount of an acetylation agent to natural dermal collagen under reaction conditions to react said natural dermal collagen with said acetylation agent to form a modified collagen, said modified collagen having higher net charge and higher net charge density than natural dermal collagen, said modified collagen for increasing one or more skin characteristics consisting of hydration, pliability and thickness

However, these shared technical features do not represent a contribution over prior art, because the shared technical features are anticipated by US 2005/0106270 A1 to Devore et al. (hereinafter Devore). Devore teaches a method of treating skin (abstract -- "the method can also be used to treat skin tissue") comprising the steps of: applying an effective amount of an acetylation agent to natural dermal collagen under reaction conditions to react said natural dermal collagen with said acetylation agent to form a modified collagen (para [0013], [0014], [0043] -- Reacting specific acylation agents with intact tissues or tissue surfaces to alter the net charge and net charge density of the treated tissue for therapeutic applications. Applying the chemical agent (acylation agent at a concentration of between 0.1 mg/mL and 100 mg/mL, preferably between 10 mg/mL and 50 mg/mL) to the exposed area such that the chemical agent immediately reacts with the tissue. The predominant protein to react with the acylation chemicals is collagen. In addition, acylation agents are applied to increase the net negative charge and the net charge density resulting in an increase in tissue hydration producing a thicker dermal skin layer with increased pliability. Finally, in an example, the skin treated was lyophilized dermis, said modified collagen having higher net charge and higher net charge density than natural dermal collagen (para [0014], [0013] -- acylation agents are applied to increase the net negative charge and the net charge density of the dermal skin layer; and the predominant protein to react with the acylation chemicals is collagen), said modified collagen for increasing one or more skin characteristics consisting of hydration, pliability and thickness (para [0014] -- acylation agents are applied to increase the net negative charge and the net charge density resulting in an increase in tissue hydration producing a thicker dermal skin layer with increased pliability).

As the shared technical features were known in the art at the time of the invention, they cannot be considered common technical features that would otherwise unify the groups. Therefore, Groups I-II lack unity under PCT Rule 13.